GUIDELINE FOR GOOD REGULATORY OVERSIGHT OF CLINICAL TRIALS BY EGYPTIAN DRUG AUTHORITY

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2 Abbreviations:

- BioInn-EDA: Central Administration of Biological and innovative products and Clinical Trials.
- CIOMS: The Council for International Organizations of Medical Sciences.
- CTA: Clinical Trial Authorization.
- CT: Clinical Trial
- CRO: Contract Research Organization.
- CRF: Case Report Form
- DSMB: Data & Safety Monitoring Board.
- EDA: Egyptian drug Authority
- FIH: First in Human.
- GA of CT: General Administration of Clinical trials
- GCP: Good Clinical Practice
- ICH: International Conference on Harmonization
- IB: Investigator's Brochure
- IMPD: Investigational Medicinal Product Dossier
- IMP: Investigational Medicinal Product.
- IRB: Institutional Review Board.
- MD: Ministerial Decree.
- MoHP: Ministry of Health and Population.
- NRA: National Regulatory Authority
- PI: Principal Investigator.
- REC: Research Ethics Committee.
- REC-RHD/MoHP: Research Ethics Committee- Research & Health Development at Ministry of Health and Population.
- NODCAR: National Organization for Drug Control and Research.
- NORCB: National Organization for Research and Control of Biologicals.
- RHD: Research & Health Development
- SAE: Serious Adverse Event.
- SUSAR: Suspected Unexpected Serious Adverse Reaction
- WHO: World Health Organization.

3 Introduction:

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The Arab Republic of Egypt has adopted the ICH GCP guidelines since 2006 by the effect of M.O.H ministerial decree no.436/2006 for the national GCP guidelines regulating the clinical trials that was already established, issued and prepared according to international GCP Guidelines and was implemented at National Organization for Research and Control of Biologicals (NORCB) and also the process for clinical trial evaluation for biologicals in EGYPT since 2010 and the former structure of the drug regulatory authority started regulating clinical trials by the effect of M.O.H ministerial decree no. 399/2010 concerning regulation for evaluation of Clinical Trials for biological products with considering the national GCP guidelines. Together with the effect of M.O.H ministerial no.734/2016 for the national GCP guidelines regulating the clinical trials of pharmaceutical products that was implemented at National Organization for Drug Control and Research (NODCAR) and also the process for clinical trial evaluation for pharmaceutical products through the effect of M.O.H ministerial decree no. 132/2017 concerning regulation for evaluation of Clinical Trials for pharmaceutical products with considering the national GCP guidelines for pharmaceutical products.

Egyptian Drug Authority (EDA) has replaced NORCB and NODCAR through the presidential decree presidential decree no (151) of (2019). EDA is engaged in a close collaborative effort with other regulatory authorities where there is strong coordination between all bodies responsible for enforcing laws and regulations relating to biological products, pharmaceutical products, medical devices, and herbal medicines to ensure that the principles of the GCP are applied.

General Administration of Clinical trials (GA of CT) is the body that is responsible for the regulatory oversight of clinical trials process through review & evaluation of the submitted preclinical and clinical data, conducting scientific committee(s), providing technical support to those who request it and is responsible for conducting GCP inspections.

The administration of Clinical Trials Evaluation is responsible for all tasks related to the review and the evaluation of clinical and pre-clinical studies through the purpose of registration, re-registration, or variations submitted to EDA in the Common technical document (CTD).

The administration of Protocols & Studies Follow up in the GA of CT is responsible for all tasks related to the supervision and following-up of clinical studies that are conducted in the Arab Republic of Egypt and evaluating their results through Evaluation of preclinical and/or clinical research results for biological, pharmaceutical, herbal and innovative investigational medicinal products and medical devices, Evaluation of the submitted file that contains the research plan (protocol) for the study of clinical research in all its phases in order to obtain approval to conduct the clinical study, Receiving periodic reports and reports on any adverse events during the study, Receiving the interim and the final report and making sure that the study is completed within the clinical research sites, carry out GCP inspection on all clinical research sites related to the study of the clinical research and to ensure the application of the principles of Good Clinical Practice and evaluation of the amendments submitted to the clinical research protocol before and/or during its conduction.

The administration of Scientific Committees and Technical Support in the GA of CT is responsible for all tasks related to EDA's advisory scientific committee for preclinical and clinical studies evaluation and technical support assistance through receiving technical support requests for evaluation, organizing and conducting the required support with the help of other

administrations if necessary and Follow-up and update the decisions and guidelines that regulate clinical trials in accordance with the international standards for good clinical practice.

This guideline was developed with consideration of the current good clinical practices and international regulations of the clinical trial data that are intended to be submitted to Egyptian regulatory authorities.

This guideline should be read in conjunction with Clinical Trials Law 214/2020 and its executive regulation and international GCP Guidelines according to ICH E6 and WHO guidelines and their updates.

4 Legal provision

- Law decree no (151) of (2019)
- Executive regulation no.777/2020 of decree no (151) of (2019).
- The Egyptian clinical trials law no. 214/2020 regulating the clinical trials in Egypt.
- EDA chairman Decree no (111) of (2022)

5 Scope:

This Guideline demonstrates for applicants (sponsor/CRO/PI) how the national GCP regulations are carried out in Egypt with clear application submission steps at different developmental phases of the investigational medicinal product.

This guideline applies to all clinical trials conducted in Egypt that are regulated by the Egyptian Drug Authority according to the Clinical Trials Law no. 214/2020 involving human participants, i.e., healthy volunteers or patients. All clinical trials that use new investigational pharmaceutical or biological medicinal products, new indications, new dosage forms, new medical devices, and herbal medicinal products are included.

6 Definitions:

Adverse Drug Reaction (ADR): In the pre-approval, clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Amendment: A written description of a change(s) to or formal clarification of a protocol.

Approval: The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Audit: A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Audit report: A written evaluation by the sponsor's auditor of the results of the audit.

Blinding/masking: A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), the investigator(s), the monitor(s), and, in some cases the data analyst(s) being unaware of the treatment assignment(s).

Case Report Form (CRF): A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject.

Clinical trial/study: Any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Clinical trial/study report: A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

Comparator (Product*):* An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

Critical GCP finding(s): Conditions, practices, or processes that adversely affect the rights, safety, or wellbeing of the subjects and/or the quality and integrity of data. Critical observations are considered totally unacceptable. Possible consequences: the rejection of data and/or legal action required. Remarks: observations classified as critical may include a pattern

of deviations classified as major, bad quality of the data, and/or absence of source documents. Manipulation and intentional misrepresentation of data belong to this group.

Contract Research Organization (CRO): A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

Documentation: All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

Good Clinical Practice (GCP): A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial subjects are protected.

Independent Ethics Committee (IEC): An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing a favorable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Informed consent*:* A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Dated Informed consent is documented by means of a written, signed, and fingerprint of that person informed consent form by a legally competent person.

Inspection: The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to

be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

Institutional Review Board (IRB): An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing a continuing review of the trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Interim clinical trial/study report: A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

Investigational product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigator's brochure: A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

Legally acceptable representative: An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

Major GCP finding(s): Conditions, practices, or processes that might adversely affect the rights, safety, or well-being of the subjects and/or the quality and integrity of data. Major observations are serious findings and are direct violations of GCP principles. - Possible consequences: data may be rejected and/or legal action required. Remarks: observations classified as major, may include a pattern of deviations and/or numerous minor observations.

Minor GCP finding (s): Conditions, practices, or processes that would not be expected to adversely affect the right, safety, or well-being of the subjects and/or the quality and integrity of data. Possible consequences: observations classified as minor indicate the need for improvement of conditions, practices, and processes. Remarks: many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

Monitoring: The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Multicenter trial: A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

Nonclinical study/Pre-clinical Research: Research conducted at an early experimental stage prior to trials on humans, which aims to specify the degrees of safety and effectiveness of the medical intervention to be studied. Pre-clinical research is conducted through in vitro tests or using experimental animals in accordance with the prescribed international standards in pre-clinical research.

Placebo: An inert product that has not therapeutic effect and completely resembles the product subject of research in form but does not contain the active substance.

Protocol: Document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol-referenced documents. Throughout the ICH GCP Guideline, the term protocol refers to protocol and protocol amendments

Randomization: The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Regulatory authorities: Bodies having the power to regulate. In the ICH GCP guideline, the expression Regulatory Authorities includes the authorities that review submitted clinical data

and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

Routine inspection: Inspection of the system and procedures used to conduct clinical research by both commercial and non-commercial organizations, in order to assure compliance with applicable legislations, protocol, procedures, guidelines & regulatory requirements. Organizations are notified of routine inspections in advance.

Serious Adverse Events (Serious ADR): Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or results in a congenital anomaly/birth defect.

Sponsor: A party that assumes responsibility for initiating, management, funding, and supervision of medical research; whether this party is a natural person such as the principal investigator or a body corporate such as a company, institution, domestic, regional, or international organization, provided, however, it is legally represented in the Arab Republic of Egypt.

Standard Operating Procedures (SOPs): Detailed, written instructions to achieve uniformity of the performance of a specific function.

Subject/trial subject: An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

The Principle Investigator: A person qualified in the field of clinical medical research and responsible for the research plan and the execution and funding thereof in case there was no sponsor available for the medical research.

The Co-Principal Investigator: A person with the same qualification of the principle investigator assigned by the latter to carry out some of his duties under his supervision. The co-principal investigator replaces the principal investigator in case of the latter's absence or inability to continue performing the research duties.

The Research Group: a group of qualified researchers working in the field of medical researches and take part in the research works based on their qualifications and expertise.

The Research Subject: A person subject of medical research who participates in the research whether that person is a patient or a healthy person and whether they are subject of medical intervention or part of the control group. In all cases; on the condition of obtaining the informed consent of the research subject before conducting the research pursuant to the provision of this law.

The Control group: A group of research subjects who do not receive the medical intervention researched; but rather receive what is called a "Placebo" or a standard treatment for the purpose of comparison and measurement of the effect of the new intervention.

The Supreme Council for Review of the Ethics of Medical Clinical Research (The Supreme Council): The council comprises a group of persons with medical and non-medical specializations and who are entrusted with the duty of establishing and following up on the general policies applicable to conducting medical research. It is referred to hereinafter as "The Supreme Council".

Trial site: The location(s) where trial-related activities are actually conducted.

Trigger inspection: These are ad hoc inspections that may be triggered as a result of NRA licensing requests or reports received by the NRA on suspected violations of legislation relating to the conduct of the clinical trials. In rare circumstances, the organization may not be notified of these inspections in advance.

Unexpected adverse drug reaction: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product)

Vulnerable subjects: Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases,

persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

7 Objective:

This guideline outlines the information required by the Egyptian Regulatory Authority from applicants (sponsors/CRO/PI) wishing to conduct clinical trials in Egypt as well as to define the evaluation process for the conduct of clinical trials and indicate the order of the material to be submitted and the minimum requirements for conducting clinical trials.

This guideline also describes the rights of the participants, the responsibilities of the Sponsor and the Principal Investigator, and the key activities in designing, conducting, monitoring, and reporting clinical trials that should be performed according to the Egyptian Clinical trials law no. 214/2020 and the Good Clinical Practice (GCP) regulations.

This detailed guideline is intended to fulfill the obligations laid down in clinical trials law no. 214/2020, and provide advice on the format, submission steps, timelines, and content of the information to be submitted to the Egyptian Drug Authority in the Arab Republic of Egypt for the applicant as per the following's roles:

a) A request for technical support for preclinical and clinical purposes during the medicinal product for human use development.

b) Evaluate the results of pre-clinical and clinical medical research.

c) Carry out the scientific review of the medicinal or biological product prior to the clinical medical research.

d) A request for Egyptian Drug Authority opinion on a proposal Research Plan "Protocol" and amendments to be conducted in Egypt, review the documents of the pharmaceutical product subject of the medical research in an endeavor to

ensure the accomplishment of the good clinical practice, proper administration, and storage

e) Notification of a substantial amendment and the request for Egyptian Drug Authority opinion on a substantial amendment,

f) Notification of the Egyptian Drug Authority on the end of the trial or early termination of the trial.

g) Submission of preclinical results for evaluation before introducing for first in human use (FIH) clinical trials.

h) Inspect the research clinical trial site(s) and other relevant entities in which clinical medical research is carried out for the purpose of verifying good clinical practices.

8 Clinical Trials Regulatory Oversight:

8.1 EDA is adopting the Principles of GCP according to ICH E6 and WHO Guidelines and all their Updates that are described as Follows

i) Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

j) Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

k) The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over the interests of science and society.

l) The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

m) Clinical trials should be scientifically sound and described in a clear, detailed protocol.

n) A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion, EDA, and supreme council approvals.

o) The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

p) Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

q) Freely given informed consent should be obtained from every subject prior to clinical trial participation.

r) All clinical trial information should be recorded, handled, and stored in a way that allows accurate reporting, interpretation, and verification.

s) The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

t) Investigational products should be manufactured, handled, stored, and disposed of in accordance with applicable good manufacturing practice (GMP) and EDA regulations. They should be used in accordance with the approved protocol.

u) Importation of Investigational products should follow EDA regulations

Systems with procedures that assure the quality of every aspect of the trial should be implemented. Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.

8.2 Submission and Evaluation of Preclinical Results before First in Human Clinical Trial (FIH)

For the purpose of evaluation of preclinical results before conducting **First In Human (FIH)** clinical trials in Egypt.

8.2.1 Evaluation Process

8.2.1.1 Screening:

The applicant shall prepare the documents including the results of preclinical studies for evaluation as per "List of Preclinical requirements: List of preclinical required documents in the file of the investigator and/or sponsor/CRO to be submitted to EDA for a scientific opinion before First in human use." before submission. The screening period will take 5 working days.

The applicant shall respond to the requirements within 5 working days. This can be renewed for another 5 working days when a suitable justification for missed or incomplete documents is submitted. The administration of Protocol and studies follow-up will reply to the applicant to perform official submission within 3 working days in case of acceptance of full package data. If the applicant does not respond to the requirements of screening, the submission will be considered rejected, and the applicant could re-submit again after at least one month.

8.2.1.2 Submission:

The applicant Should submit the screened complete preclinical file with all requirements after paying the submission fees

8.2.1.3 Evaluation:

During evaluation, requirements and/or clarification arise will be sent to the applicant The applicant should respond to all raised requirements within 15 working days or else two acceleration letters of 5 working days interval will be sent in case of delay.

It takes 60 working days after completion of all requested documents and answering all inquiries and/or clarifications raised by EDA from the applicant

8.2.1.4 EDA Final decision:

EDA will take the final decision after peer review by EDA advisory scientific committee for preclinical and clinical studies evaluation.

8.3 Submission & Evaluation of Clinical Trials Protocol &/or Amendments to EDA

8.3.1 Evaluation Process

8.3.1.1 Screening:

The applicant shall submit a clinical study protocol &/or amendments to EDA.

The official delegated person from the company shall sign and fill the application form "Applicant request to the Egyptian Drug Authority for Clinical Trial Authorization on a medicinal product for Human use"

The applicant shall satisfy all the List of required documents from the investigator, sponsor&/or CRO to be submitted to EDA as per "List of required documents from the investigator, sponsor&/or CRO to be submitted to Bio Inn-EDA for clinical trials in Egypt."

The screening period will take 5 working days. The applicant shall respond to the requirements if any within 5 working days. This can be renewed for another 5 working days when a suitable justification for any missed or incomplete documents is submitted. After that, the administration of Protocol and studies follow-up will reply to the applicant to perform official submission within 3 working days in case of acceptance of full package data. If the applicant did not respond to the requirements of screening, the submission is considered rejected and could be re-submitted after at least one month.

8.3.1.2 Submission:

The applicant will submit the screened complete CT package data after paying the relevant fees depending on the type of submission whether first submission or protocol amendments.

8.3.1.3 Evaluation:

8.3.1.3.1 During evaluation, requirements and/or clarification arise will be sent to the applicant.

The applicant should respond to all raised requirements within 15 working days or else two acceleration letters of 5 working days interval will be sent in case of delay.

It takes 60 working days starting from day 1 of submission and clock would be stopped in case of any all inquiries and/or clarifications raised by EDA.

8.3.1.3.2 EDA may rely on data, decisions, reports of stringent regulatory authority specified in accordance with the international standards by the technical committee for drug control to issue a resolution concerning evaluation and approval of clinical medical research that will be conducted in Egypt, EDA is still independent and responsible for all decision taken even if in case of relying to other stringent NRAs decisions and information approved by these bodies.

8.3.1.4 EDA Final decision:

EDA will take the final decision after peer review by EDA advisory scientific committee for preclinical and clinical studies evaluation.

** The Approval on CT conduction is valid for one year through which the applicant shall initiate the study. A renewal request should be submitted to EDA at least 30 working days before end of validity. As per “List of documents submitted for EDA Approval Renewal”.

The final decision will be raised to the supreme council for issuing final approval.

8.3.2 In Case of Amendment submission to EDA:

The applicant should notify EDA with Any deviation or change of the approved protocol and its related documents till official submission of the changed documents as amendments for approval

The applicant shall consider all the steps stated above for protocol&/amendment submission and prepare CT package data as per the List of required documents from the investigator, sponsor&/or CRO to be submitted in case of Amendment, The applicant (sponsor/PI/CRO) must notify and submit to EDA any amendments (if found) in case of changes occurring to the original protocol or any of the submitted C.T. package data or if were required by EDA, illustrating a list of changes compared to the original versions and submitting the required documents according to "List of required documents from the investigator, sponsor&/or CRO to be submitted in case of Amendment".

- If the amendment after EDA approval is judged (by the DSMB and/or Principal Investigator) as urgently necessary to protect the life or well-being of trial participants or the community, the change may be effected immediately, and the investigator must inform the IRB/IEC, EDA and supreme council within 24 hours by a written full explanation.
- If the amendment after EDA approval may affect the safety of the trial participants (e.g., changes to dose, regimen, concomitant medication, monitoring, etc.) the amendment must be submitted and approved by EDA, supreme council and IRB/IEC obtained prior to implementation.
- If the amendment after EDA approval is unlikely to impact on participant safety (e.g., change of investigator (except Principal Investigator), endpoint assay, laboratory, statistical analysis, etc.) the full detail of the change must be submitted to EDA and supreme council in writing, and the change may be implemented 14 days after receipt of the amendment by EDA if no notification to the contrary is received by the applicant.

8.3.3 In case of public health emergency:

The applicant shall submit a clinical trial protocol &/or amendments to EDA. An acceleration procedure will be taken by EDA regarding this clinical trial(s) application exhibiting a non-routine submission, as in case of parallel submission or any other measures accepted by The Supreme council & EDA with fast-track timelines.

8.4 Initiation of the Study and Reporting from the Applicant (Sponsor/ CRO)

8.4.1 Clinical medical research site activation:

The applicant (sponsor/PI/CRO) shall notify the administration of Protocols and studies follow-up upon activation of the study via email.

If the applicant activated the study without notifying EDA, the trial is subjected to suspension based on EDA recommendation.

8.4.2 Periodic reports/progress reports:

The applicant shall submit periodic follow-up progress reports (including adverse events and serious adverse events) every three months if the study period is less than a year and every six months if the study period is more than a year using the follow-up template "Follow up template".

8.4.3 Interim Clinical study report:

The applicant shall submit an interim clinical study report if applicable as per protocol.

8.4.4 Safety reports reporting:

For local Fatal or life threatening or all other expected or unexpected SAR and severe AE, EDA should be notified within 24 hours at the maximum from the notification date of PI with identifying subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses.

Then the case report of this adverse events case should be submitted within 7 days to the Egyptian drug authority

The Council for International Organizations of Medical Sciences (CIOMS) form of the adverse event cases should be submitted to EDA

In case of non-serious adverse events in phase I and II trials that are conducted in Egypt, the case report form should be submitted to EDA within 7 working days from the date the PI is notified. While in phase III and IV clinical trials that are conducted in Egypt, these adverse events should be reported in the follow up progress reports that submitted to EDA

8.4.5 Investigational Medicinal Product (IMP) Destruction:

- The applicant shall notify EDA of the date of the destruction of IMP during the ongoing CT.
- EDA Inspectors shall attend the IMP destruction procedures to ensure the correct and safe disposal as per EDA regulation.
- The applicant shall notify the Administration of Protocols and Studies Follow up after the destruction of the IMP with further evidence.

8.5 Completion of the Study

The sponsor shall notify the Administration of Protocols and Studies Follow up by email that the clinical trial has ended up and submit a summary of the trial's outcome, all information, data, and related reports of clinical medical research within 60 days of the end of the clinical trial till issuing of the final clinical study report which should be submitted to the Administration of Protocols and Studies Follow up of GA of CT at EDA for reviewing and evaluation.

8.6 Early Termination or Withdrawal of the Study by the Sponsor

8.6.1 If the trial is prematurely terminated or suspended for any reason by the sponsor, the investigator should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and as per applicable regulatory requirement(s), should inform the administration of Protocols and studies follow-up in writing within **15 working days.**

8.6.2 The applicant may request the withdrawal of his protocol/ amendment before/after EDA has reached its decision on authorization, and then a formal letter of withdrawal providing a brief description of the reasons must be submitted to EDA.

8.7 Suspension or Termination of the Study by EDA

EDA shall suspend or terminate clinical trials in Egypt that were granted EDA approval for any reasons concerning the non-GCP compliance or non-GMP compliance or SAEs or SUSAR or non-compliance with protocol after a scientific committee is held (if needed) and the reasons shall be clearly explained to the applicant. The final EDA decision is raised to the supreme council for final approval.

8.8 Inspection on Clinical Trials and Review Follow up Reports

EDA shall inspect the clinical trial site(s) and other relevant entities in which clinical medical research is carried out for the purpose of verifying good clinical practices, examining and reviewing all documents, equipment and records related to research and collecting the

necessary evidence (e.g. Documented evidences, IMP samples,….) to ensure the enforcement of the law in accordance with the applicable rules of the Egyptian Regulatory Authority.

EDA shall prepare for inspections at any step of the trial conduction whether **pre**, **during,** or **post conduction** to ensure compliance with GCP guidelines.

8.8.1 Inspection plan notification:

8.8.1.1 For routine inspection:

The inspection team prepares the inspection plan as per quality risk assessment and sends an email to the applicant at least two weeks before the stated date for inspection.

The inspection agenda and the confirmation letter of the date of proposed inspection are sent to the PI through the applicant, responsible for following up of the trial from EDA, via email to confirm with the clinical trial site where the inspection will be conducted, the date of the inspection and names of the inspectors that will carry out the inspection will be included in the confirmation letter.

The applicant shall respond with approval to the proposed inspection date.

8.8.1.2 For triggered inspection:

The inspection team may or may not notify the applicant within 24 hours before the inspection.

8.8.1.3 For follow up inspection:

Follow-up inspection can be carried out to ensure the corrective action(s) &/or preventive action(s) were implemented.

The inspection team prepares the inspection plan and sends an email to the applicant at least one week before the stated date for inspection.

8.8.2 Inspection Report:

The inspection team prepares an inspection report that includes all kinds of observations within 15 working days after completion of the inspection. Observations of inspection are classified as (critical, major, or minor).

8.8.3 Corrective action plan:

The applicant shall prepare the corrective and preventive actions plan within 20 working days from receiving the inspection report from EDA then, two acceleration letters of 5 working days interval will be sent to the applicant. In case of delay, the issue will be raised to the supreme council to take the final decision for the status of the ongoing clinical trial.

8.9 Technical Support for Preclinical and Clinical Trials

Technical support of preclinical and clinical data can make the evaluation easier and quicker because the evidence is likely to be more robust, appropriate, and complete, but it does not affect the stringent assessment of safety and efficacy.

Applicants should comply with the technical support approach, therefore, enhancing the chances of submission of preclinical results and clinical trial(s) application but it does not guarantee it.

For technical support Submission, applicants are advised to fill in the application form “Application form for technical support” and attach it with the related documents. This application helps to describe your case in an organized manner to allow for better understanding. The requests will be studied on a case-by-case basis according to the international guidelines.

8.9.1 Submission:

The company /applicant shall fill and sign the “Application form of pre-clinical and clinical technical support request”. preliminary screening is done within 10 working days. In case any document is missing after reviewing the whole submitted technical support dossier, the applicant is notified to complete it. The applicant should respond

to the letter within 10 working days, followed by two acceleration letters of 5 working days interval in case of delay.

8.9.2 Technical Support assistance:

The whole dossier of the technical support is reviewed according to the international and national guidelines within 60 working days from the date of the completion of data.

8.9.3 EDA Technical Support report:

Technical support report of Evaluation is issued and sent to the applicant.

8.10 The Principal Investigator Criteria and Responsibilities

8.10.1 The Principal Investigator Criteria

a) The Principal Investigator should meet all academic qualifications, training, and experience criteria to be able to assume the responsibility of administering medical research and to be fully acquainted with the rules and ethics of scientific research, and possess the skills deemed inevitable and necessary to deal with patients.

b) To be of good reputation.

c) Not to have been sentenced in a penal punishment or incarceration for a crime of honor or honesty unless otherwise exonerated.

d) To be free from any personal conflict of interest against conducting or completing the research or protecting the safety of any of the research subjects.

8.10.2 Responsibilities before starting the study

a) To obtain the approvals required for conducting the medical research as per CT law 214/2020.

b) To obtain the approved informed consent of research subjects or their legal representatives and document it, which shall be signed and dated by the research subject and reviewed and approved by the institutional committee.

c) To obtain approval on the research plan (protocol) of the medical research.

d) To register the research plan (protocol) in the designated database.

e) To obtain the other permits and approvals as stipulated under the law.

f) To choose an assistant to the principal investigator and members of the research team in accordance with the criteria of scientific competence.

g) To choose research subject with complete impartiality and to specify the appropriate number to conduct the medical research in accordance with the approved research plan (protocol).

8.10.3 Responsibilities during conduction of the study

a) To conduct the medical research at the clinical trial site and attend and supervise the research on regular basis; in accordance with recognized practices and standards.

b) To conform with the relevant laws and regulations and to apply the principles of good clinical practices, as well as, recognized and relevant local and international standards.

c) To manage the medical research in accordance with the research plan (Protocol) as approved by competent authorities, on a case-by-case basis.

d) The principal investigator may not cause any amendments to the research plan (Protocol) except after obtaining the approval of the entities concerned.

e) To inform research subjects of any amendments to the research plan that may affect their safety and of any unexpected risks that they or other research subjects may become exposed to, in the process of conducting the medical research.

f) To take necessary measures to protect the life, physical, psychological health, and dignity of research subjects, as well as, minimize the side effects of the medical research; including the introduction of amendments to the research plan in event of the emergence of serious side effects that may place the safety of the research subjects at risk. In such case; the principal investigator shall notify the research sponsor, institutional review board, EDA, and the Supreme Council; each in their jurisdiction of the adverse events and the procedures taken to protect the research subjects within no more than 24 hours.

g) To keep the documents of the medical research at the research facility and the premises of the research sponsor (if any) and take sufficient precautions to protect the same from any loss or damage.

h) To publish the results of the medical research in a peer-reviewed scientific journal after completion of the research.

i) To provide the necessary medical care to research subjects after completion of the medical research on a case-by-case basis whenever the principal investigator concludes the occurrence of adverse events or serious adverse events, and to notify research subjects of their need for such medical care; all for the purpose of mitigation of the harmful effects.

8.11 Responsibilities of the Sponsor/CRO

a) The Sponsor should obtain all the required approvals depending on the nature and type of the medical research.

b) To supervise the completion of the medical research and fund the research from its beginning until its completion.

c) To establish the mechanisms required for monitoring performance and quality of performance and assurance to obtaining, documenting, and publication of the results of the medical research in accordance with the approved study protocol and good clinical practices.

d) To serve the competent institutional review board and the Supreme council with periodical reports on the progress of the medical research and the funding made by the sponsor, as the case may be.

e) To enter into agreements with all parties concerned with the medical research and include these agreements in the medical research file.

f) To safe-keep with self, and in the Supreme Council's medical research database inside the Arab Republic of Egypt all the main documents and dates related to the medical research after publication of the results.

g) To provide research subjects with medical intervention during and after the completion of the medical research on a case-by-case basis and as required.

h) To immediately notify the research subjects of any modifications on the medical research, of any results that may adversely affect their safety, and of any unexpected adverse events of the medical research.

i) To conclude an insurance contract with the research subjects named as beneficiaries, and with an insurance company chartered in the Arab Republic of Egypt against any damages sustained by the research subject due to their participation in the medical research.

j) The insurance contract stated herein shall cover the entire period of the medical research and the follow-up period provided however that it shall be valid for one year after the completion of the medical research, and the insurance value shall be approved by the Supreme Council.

k) Indemnification and treatment of research subjects in case of injures related to medical research.

l) To complete the treatment of research subjects proven to need treatment after the completion of the medical research.

8.12 Key Activities that Should Comply with GCP and Related to the Design Phase

8.12.1 Development of clinical trial protocol

Clinical trials should be described in a clear, detailed protocol. The sponsor, often in consultation with one or more clinical investigators, generally designs the study protocol. Integral to protocol development are the concepts of risk identification, study design and control groups, and statistical methodology. The sponsor and clinical investigator(s) should be aware of the Egyptian clinical trial law no.214/2020

8.12.2 Development of standard operating procedures (SOPs)

All parties who oversee, conduct, or support clinical trials (i.e., sponsors, clinical investigators, Institutional Review Boards [IRBs] monitors, contract research organizations [CROs]) should develop and follow written standard operating procedures (SOPs) that define responsibilities, records, and methods to be used for study-related activities.

Sponsors should consider preparing SOPs for:

a) Developing and updating the protocol, investigator's brochure, case report forms (CRFs), and other study-related documents.

b) Shipping, handling, destruction, and accounting for all supplies of the investigational product.

c) Standardizing the activities of sponsors and study personnel (e.g., review of adverse event reports by medical experts; data analysis by statisticians).

d) Standardizing the activities of clinical investigators to ensure that trial data is accurately captured.

e) Monitoring, to ensure that processes are consistently followed and activities are consistently documented.

f) Auditing, to determine whether monitoring is being appropriately carried out and the systems for quality control are operational and effective.

Investigators should consider developing SOPs for common trial-related procedures not addressed in the protocol. These may include but are not limited to:

Communicating with the IEC/IRB; obtaining and updating informed consent; reporting adverse events; preparing and maintaining adequate records; administering the investigational product, and accounting for and disposing of the investigational product. IECs/IRBs should develop and follow written procedures for their operations, including but not limited to: membership requirements; initial and continuing review; communicating with the investigator(s) and institution; and minimizing or eliminating conflicts of interest.

8.12.3 Development of support systems and tools:

Appropriate support systems and tools facilitate the conduct of the study and collection of data required by the protocol. Support systems and tools include, but are not limited to, trial-related information documents (e.g., investigator's brochure, case report forms [CRFs], and checklists. The sponsor is generally responsible for developing support systems and tools for conducting the trial and collecting and reporting required data. For example, a diagnostic or laboratory equipment specified in the study protocol, and procedures/schedules for servicing the equipment according to the manufacturer's specifications; computer systems (hardware and software) to be used in the clinical trial (e.g., statistical or other software, electronic patient diaries, coding of personal data), and software validation systems, as needed; facsimile or other communications equipment to facilitate reporting of serious adverse events; information and training tools for clinical investigators and site personnel.

8.12.4 Generation and approval of trial-related documents:

Development of trial-related documents may facilitate the conduct of the study, collection and reporting of study-related data, and analysis of study results. The sponsor generally develops, designs, and provides various standardized forms and checklists to assist the clinical investigator and his/ her staff in capturing and reporting data required by the protocol.

Examples of trial information documents include, but are not limited to:

a) Investigator's Brochure.

b) Checklists to identify and document the required steps for each of the various clinical trial activities (e.g., investigator selection, approvals and clearances, monitoring, adverse event reporting and evaluation, analysis of interim data).

c) Investigational supplies accountability forms to document the amount and source of investigational product shipped and received, the amount dispensed to subjects, and the return/destruction, as appropriate, of any unused product.

d) Signature logs and other forms to document by whom activities are completed, when, and the sequence in which they are carried out.

e) Case report forms (CRFs) for each scheduled study visit to capture all of the necessary data collected from and reported for each subject.

f) Informed consent documents.

g) Adverse events or safety reporting forms.

h) Administrative forms to track research funds and expenses.

i) Forms to disclose information about the investigator's financial, property, or other interests in the product under study, in accordance with national/local law or regulations.

j) Formats for reports of monitoring visits.

k) Formats for progress reports, annual reports, and final study reports

Selection of trial sites and the selection of properly qualified, trained and experienced investigators and study personnel.

8.13 Key Activities that Should Comply with GCP and Related to the Conduction Phase

8.13.1 Enrollment of subjects into the study: recruitment, eligibility, and informed consent.

The clinical investigator has primary responsibility for recruiting subjects, ensuring that only eligible subjects are enrolled in the study, and obtaining and documenting the informed consent of each subject. Within GCP, informed consent must be obtained from each study subject prior to enrollment in the study or performing any specific study procedures

8.13.2 The investigational product(s): quality, handling, and accounting.

Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP) and EDA regulations. They should be used in accordance with the approved protocol. GCP requires that sponsors control access to the investigational product and also document the quantity(ies) produced, to whom the

product is shipped, and disposition (e.g., return or destruction) of any unused supplies. Destruction & disposition of investigational products should be conducted as per EDA regulations.

8.13.3 Trial data acquisition: conducting the trial.

Research should be conducted according to the approved protocol and applicable regulatory requirements. Study records documenting each trial-related activity provide critical verification that the study has been carried out in compliance with the protocol.

8.13.4 Safety management and reporting.

All clinical trials must be managed for safety. Although all parties who oversee or conduct clinical research have a role/responsibility for the safety of the study subjects, the clinical investigator has primary responsibility for alerting the sponsor, the IEC/IRB, EDA, and the supreme council to adverse events, particularly serious/life-threatening unanticipated events, observed during the course of the research. The sponsor, in turn, has primary responsibility for reporting of study safety to regulatory authorities and other investigators and for the ongoing global safety assessment of the investigational product. A data and safety monitoring board (DSMB) may be constituted by the sponsor to assist in overall safety management.

8.13.5 Monitoring the trial

Sponsors generally perform site monitoring of a clinical trial to assure high-quality trial conduct. The sponsor may perform such monitoring directly or may utilize the services of an outside individual or organization (e.g., contract research organization [CRO]). The sponsor determines the appropriate extent and nature of monitoring based on the objective, purpose, design, complexity, size, blinding, and endpoints of the trial, and the risks posed by the investigational product. The “on-site” monitors review individual case histories in order to verify adherence to the protocol, ensure the ongoing implementation of appropriate data entry and quality control procedures, and verify adherence to GCP. In blinded studies, these monitors remain blinded to study arm assignment.

8.13.6 Managing trial data

Within GCP, managing clinical trial data appropriately assures that the data are complete, reliable, and processed correctly, and that data integrity is preserved. Data management includes all processes and procedures for collecting, handling, manipulating, analyzing, and storing/archiving of data from study start to completion. The sponsor bears primary responsibility for developing appropriate data management systems. The sponsor and the investigator share responsibility for implementing such systems to ensure that the integrity of trial data is preserved.

8.13.7 Quality assurance of the trial performance and data

Quality assurance (QA) verifies through systematic, independent audits that existing quality control systems are working and effective. Quality assurance audits may be performed during the course of the clinical trial and/or upon trial completion.

Sponsors bear primary responsibility for establishing quality systems and conducting quality assurance audits.

8.14 General Considerations

8.14.1 According to the Egyptian clinical trials law no. 214/2020 article 10, the allowed CT applications for submission to EDA as follows:

- For nationally originated interventions, all phases of clinical trials **(I, II, III, and IV)** are allowed to be conducted in Egypt on the condition that the results of each stage are reviewed and EDA approves to move forward to the next clinical phase.
- For the medical interventions that arise outside the Arab Republic of Egypt, clinical trial phases III and IV are allowed after review and approval by the EDA and the Supreme Council of the results of the clinical trial phases I and II, which were conducted in the country of origin.

- ❖ As an exemption from this condition; is the medical intervention for endemic diseases that do not exist in the country of the origin of the medical intervention and rare diseases, in which case medical research for cases is allowed in the Arab Republic of Egypt beginning from the clinical trial phase II and subject to the approval of the Supreme Council.

8.14.2 Other Authorities involved in the decision of the CT application:

- IRB approval.
- Supreme council: it is a must to acquire supreme council final approval.
- General Intelligence Agency opinion shall be obtained in case the research is being conducted with foreign entities and in case of jointly conducted international trials.
- Drug control entities and other relevant entities' opinions shall be obtained in accordance with the Egyptian CT law no. 214/2020.

9 References:

- European Medicines Agency EMA, Committee for Medicinal Products for Human Use, ICH. ICH guideline E6 on good clinical practice (Draft ICH E6 principles). Eur Med Agency EMA [Internet]. 2021; EMA/CHMP/I(337843/2021):1–8. Available from: www.ema.europa.eu/contact
- European Medicines Agency (EMA). Guideline Good Clinical Practice E6(R2). Comm Hum Med Prod. 2018;6(December 2016):1–68.
- Handbook for good clinical research practice (GCP): guidance for implementation. World Health Organization, 2005.
- Medicines Agency E. Procedure for reporting of GCP inspections requested by the Committee for Medicinal Products for Human Use (CHMP) GCP Inspectors Working Group. 2016;44(March):18. Available from: www.ema.europa.eu
- Detailed guidance on the request to the competent authorities for authorization of a clinical trial on a medicinal product for human use, the notification of substantial amendments, and the declaration of the end of the trial (2010).
- Clinical trials law no. (214) of 2020.
- EDA chairman Decree no (111) of(2022)
- Law decree No (151) of (2019)
- EDA decision No (66) of (2020) for regulations of procedures of importation and customs release of medicinal products
- Importation and Customs release guidance 2021
- Ministerial decree No. 399 of 2010.
- Ministerial decree no.436/2006.
- Ministerial decree no.132/2017.
- Ministerial no.734/2016.

10 Template forms:

10.1 List of Preclinical requirements: List of preclinical required documents in the file of the investigator and/or sponsor/CRO to be submitted to EDA for scientific opinion before First in human use.

10.2 Application form "Applicant request to the Egyptian Drug Authority for Clinical Trial Authorization on a medicinal product for human use".

10.3 List of documents submitted for EDA Approval Renewal

10.4 List of required documents from the investigator, sponsor&/or CRO to be submitted to Bio Inn-EDA for clinical trials in Egypt

10.5 List of required documents from the investigator, sponsor&/or CRO to be submitted in case of Amendment.

10.6 Follow up template

10.7 Application form for technical support

- All these forms are available on the EDA website and should be checked regularly for updates.